Drug Monograph

Drug Name: **Livmarli™ (maralixibat) oral solution**
Drug Class: **Gastrointestinal: Bile Salt Agents**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Livmarli is available as an oral solution containing 9.5 mg of maralixibat per mL.
Manufacturer:	Distributed by: Mirum Pharmaceuticals, Inc., Foster City, CA 94404.
Summary of Findings:	The ICONIC study was a long-term clinical trial to evaluate the safety and efficacy of Livmarli which involved six parts: 6-week open-label dose-escalation period; 12-week open-label stable-dosing period; 4-week randomized, double-blind, placebo-controlled drug-withdrawal period; 26-week long-term stable-dosing period; 52-week optional follow-up treatment perio; and an optional long-term follow-up treatment period (for eligible participants).The primary endpoint was the change from Week 18 to Week 22 in fasting serum bile acid (sBA) levels in participants with a reduction in sBA ≥50% from baseline to Week 12 or Week 18. Few patients met the prespecified sBA reduction criteria: • Livmarli (n=5): least squares (LS) mean (SE) sBA level µmol/L was -21.73 (43.125) • Placebo (n=10): LS mean (SE) sBA level µmol/L was 95.55 (30.488). Key secondary outcomes were the change in pruritus as measured by the Itch Reported Outcome Instrument (ItchRO™) by the observer and by the patient, and the change from baseline to Week 18 in fasting sBA levels.
Status Recommendation:	☐ Clinical Edit ☐ PA Required ☐ Open Access ☒ PDL
Type of PA Criteria:	☐ Appropriate Indications ☒ Non-Preferred ☐ No PA Required ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2,4-8]

Alagille syndrome (ALGS) is an autosomal dominant, multisystem disorder associated with abnormalities of the liver, heart, bones, eyes, and kidneys. Presentation of Alagille syndrome can vary greatly between individuals, even among family members sharing the same pathogenic variant. Alagille syndrome is caused by pathogenic variants in the JAG1 gene (90% of cases) and the NOTCH2 gene (1% of cases). The estimated incidence of ALGS is 1 in 30,000 to 1 in 45,000 in the United States. Alagille syndrome most commonly affects the liver with symptoms presenting during the first 3 months of life including cholestasis, jaundice, pruritis, xanthomas, and failure to thrive due to improper fat absorption. Severity can range from asymptomatic elevations in liver enzymes to cirrhosis and end-stage liver disease. Approximately 75-90% of patients with ALGS have a reduced number (paucity) of bile ducts often leading to cholestasis. Severe pruritis often results in scarring, bleeding, excoriations, and discomfort leading to an impact on quality of life. The exact mechanism by which cholestasis causes pruritis is not fully understood. Theories implicate elevated venous histamine levels, retention of pruritogenic intermediates in bile acid synthesis, and elevated serum bile acid levels.

Fat-soluble vitamins (FSV) require bile acid to be properly absorbed in the intestines. Patients with ALGS often present with FSV deficiency which can result in vision problems (vitamin A), bone weakness (vitamin D), developmental delay (vitamin E), and clotting problems (vitamin K). Cardiac abnormalities range from benign heart murmurs to structural defects and occur in 90-97% of patients with ALGS, with stenosis/hypoplasia of the pulmonary arteries being most common. Skeletal abnormalities include a wide range of vertebral anomalies. The most common are butterfly vertebrae, where the anterior arches of vertebrae fail to fuse. Butterfly vertebrae do not result in symptoms but can be useful in diagnosis of ALGS. Distinct facial features are observed in ALGS patients and include a high forehead, deep-set eyes, pointed chin, and a straight nose with a bulbous tip. These facial features appear to occur in the presence of the JAG1 pathogenic variant. Diagnosis can be established by genetic testing confirming the presence of JAG1 or NOTCH2 pathogenic variants, however a very small percentage of patients with ALGS do not present with one of these variants. Clinical criteria for diagnosis include having three of the following five clinical manifestations: cholestasis, cardiac defects, skeletal abnormalities, ocular abnormalities, and distinctive facial features.

Dosage Form [3]

Livmarli is available as an oral solution containing 9.5 mg of maralixibat per mL.

Manufacturer [3]

Distributed by: Mirum Pharmaceuticals, Inc., Foster City, CA 94404.

Indication(s) [3]

Livmarli is indicated for the treatment of cholestatic pruritus in patients with ALGS 1 year of age and older.

Clinical Efficacy [3,4,5] (mechanism of action/pharmacology, comparative efficacy)

Livmarli is a reversible inhibitor of the ileal bile acid transporter (IBAT). It decreases the reabsorption of bile acids (primarily the salt forms) from the terminal ileum. ALGS cholestasis is associated with increased serum bile acid (sBA), a reduction of sBA reduces bile acid-mediated cholestatic symptoms.

Pharmacokinetics:

Absorption	N/A
Metabolism	N/A
Excretion	Fecal (73%), Renal (0.066%)
Half-life	1.6 hours

Clinical Trials Experience

STUDY DESIGN (NCT02160782)	Open-label Phase 2 ICONIC study with a double-blind, placebo-controlled randomized drug withdrawal period (N=31)
INCLUSION CRITERIA	• Age between 12 months and 18 years • Diagnosis of ALGS • Evidence of cholestasis (one or more of the following): • Total serum bile acid (sBA) > 3x upper limit of normal (ULN) for age • Conjugated bilirubin > 1 mg/dL • FSV deficiency otherwise unexplainable • Gamma-glutamyl transferase (GGT) > 3x ULN for age • Intractable pruritis explainable only by liver disease • Average daily score > 2 (moderate pruritis symptoms) on the Itch Reported Outcome (ItchRO) questionnaire for two consecutive weeks in the screening period
EXCLUSION CRITERIA	• Previous liver transplant or surgical interruption of the enterohepatic circulation • Pregnancy • Decompensated cirrhosis or other concomitant liver disease • History or presence of gallstones or kidney stones • Chronic diarrhea requiring intravenous fluid or nutritional intervention • Known diagnosis of human immunodeficiency virus (HIV) infection • Cancer, except for in situ carcinoma, or cancers treated at least 5 years prior to screening with no evidence of recurrence • Administration of bile acid or lipid binding resins within 28 days prior to screening and throughout trial • Participants weighing over 50 kg at screening
TREATMENT REGIMEN	Patients were administered open-label treatment with Livmarli 380 mcg/kg once daily for 13 weeks after an initial 5-week dose-escalation period. Two patients discontinued during the first 18 weeks of open-label treatment. The 29 patients who completed the open-label treatment phase were then randomized to continue treatment with Livmarli or receive matching placebo during the 4-week drug withdrawal period at weeks 19-22. All 29 patients completed the randomized, blinded drug withdrawal period and subsequently

<table>
<tr><td></td><td>received open-label Livmarli 380 mcg/kg once daily for an additional 26 weeks.</td></tr>
<tr><td>RESULTS</td><td>

Primary Outcome Measure: change from week 18 to week 22 in fasting sBA levels in participants who had a reduction in sBA ≥50% from baseline to week 12 or week 18 (modified intent-to-treat [MITT] population). Five participants in the Livmarli group and 10 participants in the placebo group met the prespecified sBA reduction criteria.

<table>
<tr><th></th><th>Livmarli 380mcg/kg/day</th><th>Placebo</th></tr>
<tr><td>Number of participants</td><td>5</td><td>10</td></tr>
<tr><td>Least Square Mean[1] (Standard Error) Unit of Measure: µmol/L</td><td>-21.73 (43.125)</td><td>95.55 (30.488)</td></tr>
</table>
[1]The difference between treatment groups in change from Week 18 to Week 22 in fasting sBA levels was evaluated using an analysis of covariance (ANCOVA) model with treatment group as a factor, and Week 18 sBA as a covariate.

Secondary Outcome Measure: change from week 18 to week 22 in pruritis as measured by ItchRO(Obs) weekly average. The ItchRO(Obs) outcome is used to measure a participant's pruritis as observed by their caregiver twice daily (once in the morning and once in the evening). Pruritis symptoms were assessed on a 5-point scale, with scores ranging from 0 (no reported symptoms) to 4 (very severe). The average of the worst daily ItchRO(Obs) was computed for each week. For randomized patients, the mean (SD) at baseline was 3.1 (0.5) and the mean (SD) at week 18 was 1.4 (0.9). Participants aged 5 years or older were able to self-report their itching severity. Participants who were administered Livmarli through week 22 maintained pruritis reduction. Participants in the placebo group returned to baseline pruritis scores by week 22.

<table>
<tr><th></th><th>Livmarli (N=13)</th><th>Placebo (N=16)</th><th>Mean Difference</th></tr>
<tr><td>Week 22, Mean (95% CI)</td><td>1.6 (1.1, 2.1)</td><td>3.0 (2.6, 3.5)</td><td></td></tr>
<tr><td>Change from Week 18 to Week 22, Mean (95% CI)</td><td>0.2 (-0.3, 0.7)</td><td>1.6 (1.2, 2.1)</td><td>-1.4 (-2.1, -0.8)</td></tr>
</table>
Abbreviations: CI = Confidence Interval
Results based on an analysis of covariance model with treatment groups and Week 18 average worst daily pruritis score as covariates
</td></tr>
<tr><td>SAFETY</td><td>Discussed in the Adverse Effects section below.</td></tr>
</table>

Contraindications (3,4)

- None

Warnings and Precautions (3,4)

- Liver Test Abnormalities: Obtain baseline liver tests and monitor during treatment. Dose reduction or treatment interruption may be considered if abnormalities occur. For persistent or recurrent liver test abnormalities, consider Livmarli discontinuation.
- Gastrointestinal Adverse Reactions: Consider interrupting Livmarli treatment if a patient

experiences persistent diarrhea, abdominal pain, vomiting, or has diarrhea with bloody stool, vomiting, dehydration requiring treatment, or fever. If diarrhea, abdominal pain, or vomiting persists and no alternate etiology is identified, consider stopping Livmarli treatment.

- Fat-soluble Vitamin (FSV) Deficiency: Obtain baseline levels and monitoring during treatment. Supplement if deficiency is observed. If FSV deficiency persists or worsens despite FSV supplementation, consider discontinuing Livmarli treatment.

Adverse Effects (3,4)

LIVMARLI (N=86)		
Most common, ≥5%	**Any Grade (n) %**	**Number of events per 100 person-years[1]**
Diarrhea	48 (55.8%)	41.6
Abdominal pain*	46 (53.5%)	38.6
Vomiting	35 (40.7%)	19.8
Nausea	7 (8.1%)	2.9
Fat-soluble vitamin deficiency*	22 (25.6)	11.1
Transaminases increased (ALT, AST)*	16 (18.6)	6.9
Gastrointestinal bleeding*	9 (10.4%)	3.8
Bone fractures*	8 (9.3%)	3.3

*Terms were defined as:

- FSV deficiency includes: vitamin A, D, E, or K deficiency, or INR increase
- Abdominal Pain includes: abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper
- Transaminase increased includes: ALT abnormal, ALT increased, AST abnormal, AST increased
- Gastrointestinal Bleeding includes: hematochezia, hematemesis, gastrointestinal hemorrhage, melena
- Bone Fracture includes: tibia fracture, hand fracture, humerus fracture, pathological fracture, forearm fracture, clavicle fracture

[1]Exposure adjusted incidence rate for each adverse reaction type was calculated using the first occurrence of this adverse reaction per patient.

Drug Interactions (3,4)

- Bile Acid Binding Resins: Resins may bind to Livmarli in the gut. Administer resins at least 4 hours before or after administration of Livmarli.
- OATP2B1 Substrates: Livmarli is an OATP2B1 inhibitor based on in vitro studies. A decrease in the oral absorption of OATP2B1 substrates (e.g., statins) due to OATP2B1 inhibition in the GI tract cannot be ruled out. Consider monitoring the drug effects of OATP2B1 substrates as needed.

Dosage and Administration (3,4)

The recommended dosage is 380 mcg/kg once daily, taken 30 minutes before the first meal of the day. Start dosing at 190 mcg/kg administered orally once daily; after one week, increase to 380 mcg/kg once daily, as tolerated. The maximum daily dose volume for patients above 70 kg is 3 mL or 28.5 mg per day. See table below for weight-based dosing guidelines.

Patient Weight (kg)	Days 1-7 (190 mcg/kg once daily)		Beginning Day 8 (380 mcg/kg once daily)	
	Volume QDay (mL)	Dosing dispenser size (mL)	Volume QDay (mL)	Dosing dispenser size (mL)
5 to 6	0.1	0.5	0.2	0.5
7 to 9	0.15		0.3	
10 to 12	0.2		0.45	
13 to 15	0.3		0.6	1
16 to 19	0.35		0.7	
20 to 24	0.45		0.9	
25 to 29	0.5		1	
30 to 24	0.6	1	1.25	3
35 to 39	0.7		1.5	
40 to 49	0.9		1.75	
50 to 59	1		2.25	
60 to 69	1.25	3	2.5	
70 or higher	1.5		3	

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/ Month
Maralixibat	Livmarli™	Mirum Pharmaceuticals	Titrate to 380 mcg/kg/dose daily 30 min. before the first meal of the day	$33,000 based on 17 kg patient
Odevixibat	Bylvay™	Albireo Pharma	40 mcg/kg/dose daily in the am for patients ≥19.5 kg; max 120 mcg/kg/day	$32,000 based on 18 kg patient
Ursodiol	Actigall®	Various	15 to 30 mg/kg/day	$89
Cholestyramine	Questran®	Various	4 g orally 1 to 2 times daily before meals	$246

** Wholesale Acquisition Cost

Conclusion

Livmarli is the first and only FDA-approved medication for cholestatic pruritus associated with ALGS, which is often resistant to treatment. Prior to Livmarli approval, treatment consisted of a variety of anti-pruritus medications, including ursodiol and cholestyramine as first-line agents. Approval was based on the ICONIC trial; however, the study provides limited evidence of benefiting the patients in either reduction of sBA or reducing the itching using the ItchRO scale. The most common adverse reactions were diarrhea, abdominal pain, vomiting, and FSV deficiency. Considering that the majority (90.3%) of the patients in the ICONIC study were receiving at least 1 medication to treat pruritus, it is reasonable to require a prior authorization on Livmarli including a trial and failure of multiple older and less expensive options.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List (PDL) as non-preferred.

References

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